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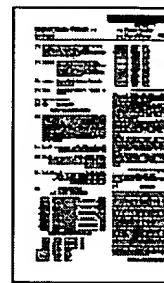
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>Title: **US6063759: Conjugate of biologically active compound and polar lipid conjugated to a microparticle for biological targeting**
 [[Derwent Title](#)]

Country: US United States of America

Inventor: **Yatvin, Milton B.**; Portland, OR
Stowell, Michael H B; Fulbourn, United Kingdom
Gallicchio, Vincent S.; Lexington, KY
Meredith, Michael J.; Lake Oswego, OR



Assignee: **Oregon Health Sciences University**, Portland, OR
 other patents from **OREGON HEALTH SCIENCES UNIVERSITY**
 (420630) (approx. 161)
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Published / Filed: **2000-05-16 / 1998-04-14**

Application Number: **US1998000060011**

IPC Code: **A01N 37/18; A61K 9/127; A61K 47/00; C12N 5/08; C07K 17/00;**

ECLA Code: **C07H19/06E; C07H19/10E;**

U.S. Class: **514/002; 424/450; 435/176; 435/178; 435/179; 435/180; 435/325; 435/366; 530/300; 530/329; 530/331; 530/811; 530/813; 530/814; 530/815;**

Field of Search: **514/002 424/450 536/051,78,28.2 436/518,528
 530/300,331,329,810,815,811,813,814
 435/174,180,325,366,176,178,179**

Government Interest: This invention was made with government support under grant 1-R01-CA49416 by the National Institutes of Health. The government has certain rights in the invention.

Priority Number: **1998-04-14 US1998000060011
 1996-08-01 US1996000691891
 1995-05-16 US1995000441770
 1994-05-19 US1994000246941
 1993-10-26 US1993000142771
 1992-07-09 US1992000911209
 1990-11-01 US1990000607982**

Abstract: Methods and reagents are provided for specifically targeting biologically active compounds such as antiviral and antimicrobial drugs, or prodrugs containing the biologically active compound to specific sites such as specific organelles in phagocytic mammalian cells. The biologically active compound or prodrug is linked to a

microparticle with a linker that is non-specifically or specifically cleaved inside a phagocytic mammalian cell. Alternatively, the biologically active compound or prodrug is impregnated into a porous microparticle or coated on a nonporous microparticle, and then coated with a coating material that is non-specifically or specifically degraded inside a phagocytic mammalian cell. The prodrug contains the biologically active compound linked to a polar lipid such as ceramide with a specific linker such as a peptide that is specifically cleaved to activate the prodrug in a phagocytic mammalian cell infected with a microorganism. A microparticle linked antimicrobial drug or prodrug may be used for killing a microorganism infecting a phagocytic mammalian cell in vivo or in vitro.

❑ Attorney, Agent or Firm:

McDonnell Boehnen Hulbert & Berghoff ;

❑ Primary /

Assistant

Examiners:

❑ INPADOC

Legal Status:

Naff, David M.;

None [Buy Now: Family Legal Status Report](#)

❑ Related Applications:

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Application Number	Filed	Patent	Pub. Date	Title
US1996000691891	1996-08-01	US5840674	1998-11-24	Covalent microparticle-drug conjugates for biological ta
US1995000441770	1995-05-16	US5543391	1996-08-06	Covalent microparticle-drug conjugates for biological ta
US1994000246941	1994-05-19	US5543390	1996-08-06	Covalent microparticle-drug conjugates for biological ta
US1993000142771	1993-10-26	US5543389	1996-08-06	Covalent polar lipid-peptide conjugates for use in salve
US1992000911209	1992-07-09	US5256641	1993-10-26	Covalent polar lipid-peptide conjugates for immunologic targeting
US1990000607982	1990-11-01	US5149794	1992-09-22	Covalent lipid-drug conjugates for drug targeting

❑ Parent Case:

This application is a continuation of application Ser. No. 08/691,891, filed Aug. 1, 1996, now U.S. Pat. No. 5,840,674, which is a continuation of application Ser. No. 08/441,770, filed May 16, 1995, now U.S. Pat. No. 5,543,391, which is a continuation of application Ser. No. 08/246,941, filed May 19, 1994, now U.S. Pat. No. 5,543,390, which is a continuation-in-part of application Ser. No. 08/142,771, filed Oct. 26, 1993, now U.S. Pat. No. 5,543,389, which is a continuation-in-part of application Ser. No. 07/911,209, filed Jul. 9, 1992, now U.S. Pat. No. 5,256,641, which is a continuation-in-part of application Ser. No. 07/607,982, filed Nov. 1, 1990, now U.S. Pat. No. 5,149,794, the disclosures of each of which are herein incorporated by reference in its entirety.

❑ Designated Country:

AM AP BB BG BR BY CA CN CZ EE FI GE HU IS KE KG KP KR KZ LK LR LT LV BE FR GB GR IE IT LI LU MC

Family: [Show 24 known family members](#)

First Claim: [Show all 69 claims](#)

What is claimed is:

1. A composition of matter comprising a prodrug of a biologically-active compound, a microparticle and a cleavable linker moiety comprising two linker functional groups, wherein the cleavable linker moiety has a first end and a second end and wherein the microparticle is attached to the first end of the linker moiety through a first linker functional group and the prodrug attached to the second end of the linker moiety through a second linker functional group, and wherein the cleavable linker moiety is non-specifically cleaved inside a phagocytic mammalian cell, and wherein the prodrug comprises a biologically active compound, a polar lipid moiety comprised of one or a plurality of polar lipid molecules and a specific linker moiety, wherein the specific linker moiety is covalently linked to both the biologically active compound and the polar lipid moiety, wherein the specific linker moiety is specifically cleaved in a phagocytic mammalian cell infected with a microorganism and is specifically activated thereby.

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Buy PDF	Patent	Pub.Date	Inventor	Assignee	Title
	US4780455	1988-10	Liberman et al.	The Trustees of Columbia University in the City of New York	Lipophilic comp pharmacologica organic compou
	US4793986	1988-12	Serino et al.	Johnson Matthey, Inc.	Macromolecula antitumor comp
	US4847240	1989-07	Ryser et al.	The Trustees of Boston University	Method of effec uptake of molec
	US5053394	1991-10	Ellestad et al.	American Cyanamid Company	Targeted forms methyltrithio an agents
	US5149794	1992-09	Yatvin et al.	State of Oregon	Covalent lipid-d conjugates for d targeting
	US5256641	1993-10	Yatvin et al.	State of Oregon	Covalent polar peptide conjuga immunological t
	US5258453	1993-11	Kopecek et al.	University of Utah	Drug delivery sy the simultaneou of drugs activat enzymes and lig
				State of Oregon, Acting by and Through the Oregon State	Covalent polar

 US5543389	1996-08	Yatvin et al.	Board of Higher Education on Behalf of the Oregon Health Sciences University, a non profit organization	peptide conjugates in salves
 US5543390	1996-08	Yatvin et al.	State of Oregon, Acting by and Through the Oregon State Board of Higher Education, Acting for and on Behalf of the Oregon Health Sciences University	Covalent microp drug conjugates biological target
 US5543391	1996-08	Yatvin et al.	State of Oregon, Acting by and Through the Oregon State Board of Higher Education, Acting for and on Behalf of the Oregon Health Sciences University	Covalent microp drug conjugates biological target
 US5840674	1998-11	Yatvin et al.	Oregon Health Sciences University	Covalent microp drug conjugates biological target

Foreign References:

Buy PDF	Publication	Date	IPC Code	Assignee	Title
 EP0077529	1983-04	C07C 93/187	Sanol Schwarz GmbH	Medicinal form	
 EP0109484	1983-04	G08B 21/00	Trampnau, Ulrich	Warning device for helicopters	
 EP0203676	1986-12	A61K 39/12	THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY	Vaccine for generating immunogenic response protein against a virus	
 EP0279887	1988-08	C07C 101/30	Kesner, Leo	Carnitine direct pharmaceuticals and their use for manufacture of medicament for treatment of metabolic disorder	
 WO8911299	1989-11	A61K 49/00	STATE OF OREGON acting by and through THE STATE ...	METHOD FOR DELIVERY OF THERAPEUTIC AGENTS TO TARGET TISSUE USING MONOCLONAL ANTIBODY CONJUGATES	
 WO8910348	1989-11	C07C 99/10	GIBBONS, William, Anthony	FATTY AMINO ACIDS AND HOMO-A HETERO-OLIGOMERIC CONJUGATES THEREOF	
 WO9000555	1990-01	C07H 15/12	VICAL, INC.	LIPID DERIVATIVES ANTIVIRAL NUCLEOSIDE LIPOSOMAL INCORPORATION METHOD OF	
					COVALENT CONJUGATES

<input checked="" type="checkbox"/>	<u>WO9010448</u>	1990-09	A61K 31/70	GENENTECH, INC.	<u>AND OLIGONUCLE</u> <u>LIPID A</u> <u>ANALOG/IMM</u> <u>CARRIER CO</u> <u>AND THE USE</u> <u>AS VACCINES</u>
<input checked="" type="checkbox"/>	<u>WO9101750</u>	1991-02	A61K 39/02	UNIVAX BIOLOGICS INCORPORATED	<u>CATIONIC LIP</u> <u>INTRACELLU</u> <u>DELIVERY OF</u> <u>BIOLOGICALL</u> <u>MOLECULES</u>
<input checked="" type="checkbox"/>	<u>WO9116024</u>	1991-10	A61F 13/00	VICAL, INC.	<u>ETHER LIPID-</u> <u>NUCLEOSIDE</u> <u>COVALENT</u> <u>CONJUGATES</u>
	<u>WO9119726A</u>	1991-12	C07H 17/00	KUCERA, Louis, S.	<u>TRANSVASCU</u> <u>INTRACELLU</u> <u>DELIVERY OF</u> <u>PROTEINS</u>
<input checked="" type="checkbox"/>	<u>WO9401131</u>	1994-01	A61K 39/00	EUKARION, INC.	<u>COVALENT P</u> <u>LIPID-PEPTID</u> <u>CONJUGATES</u> <u>BIOLOGICAL</u> <u>TARGETING</u>
<input checked="" type="checkbox"/>	<u>WO9401138</u>	1994-01	A61K 47/48	STATE OF OREGON, acting by and through the OREGON STATE BOARD OF HIGHER EDUCATION on behalf of the OREGON HEALTH SCIENCES UNIVERSITY	<u>TARGETING O</u> <u>LIPOSOMES T</u> <u>BLOOD-BRAIN</u> <u>BARRIER</u>
<input checked="" type="checkbox"/>	<u>WO9402178</u>	1994-02	A61K 47/48	THE GOVERNMENT OF THE UNITED STATES OF AMERICA as	<u>COMPOUND</u> <u>OF INTRACER</u> <u>RESIDENCE A</u> <u>THEREOF</u>
<input checked="" type="checkbox"/>	<u>WO9403424</u>	1994-02	C07C 323/41	DRUG DELIVERY SYSTEM INSTITUTE, LTD.	<u>BRAIN-ENHAN</u> <u>DELIVERY OF</u> <u>NEUROACTIV</u> <u>PEPTIDES BY</u> <u>SEQUENTIAL</u> <u>METABOLISM</u>
<input checked="" type="checkbox"/>	<u>WO9406450</u>	1994-03	A61K 37/00	UNIVERSTIY OF FLORIDA	<u>CELL-TARGE</u> <u>PORE-FORMI</u> <u>AGENTS</u>
<input checked="" type="checkbox"/>	<u>WO9425616</u>	1994-11	C12P 21/00	WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY	<u>BLOOD-BRAIN</u> <u>TRANSPORTE</u> <u>NEUROLOGIC</u> <u>AGENTS</u>
<input checked="" type="checkbox"/>	<u>WO9507092</u>	1995-03	A61K 38/00	THE UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JE	<u>DRUG TARGE</u> <u>SYSTEM, MET</u> <u>PREPARINGS</u> <u>ITS USE</u>
<input checked="" type="checkbox"/>	<u>WO9522963</u>	1995-08	A61K 9/51	MEDINOVA MEDICAL CONSULTING GMBH	<u>COVALENT</u> <u>MICROPARTI</u> <u>CONJUGATES</u> <u>BIOLOGICAL</u> <u>TARGETING</u>
<input checked="" type="checkbox"/>	<u>WO9532002</u>	1995-11	A61K 47/48	STATE OF OREGON, acting by and through THE OREGON STATE BOARD OF HIGHER EDUCATION ON BEHALF OF THE OREGON HEALTH	

				SCIENCES UNIVERSITY	
	WO9604001	1996-02	A61K 38/00	MOLECULAR/STRUCTURAL BIOTECHNOLOGIES, INC.	SITE-SPECIFI BIOMOLECUL COMPLEXES
	WO9622303	1996-07	C07J 5/00	BENDER, Veronika, Judith	THERAPEUTI COMPOUND ACID CONJUG

Other Abstract Info: CHEMABS 118(04)027456V CHEMABS 120(24)307470P CHEMABS 124(14)185548E 125(16)204546S CHEMABS 125(18)230787R CHEMABS 129(25)335730C DERABS C 340298 DERABS C1993-350862 DERABS C1996-020359

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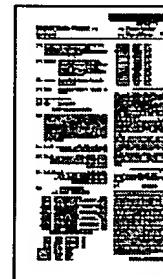
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>Title: **US6063759: Conjugate of biologically active compound and polar lipid conjugated to a microparticle for biological targeting**
 [[Derwent Title](#)]

Country: **US United States of America**

Inventor: **Yatvin, Milton B.; Portland, OR**
Stowell, Michael H B; Fulbourn, United Kingdom
Gallicchio, Vincent S.; Lexington, KY
Meredith, Michael J.; Lake Oswego, OR



Assignee: **Oregon Health Sciences University, Portland, OR**
 other patents from [OREGON HEALTH SCIENCES UNIVERSITY \(420630\)](#) (approx. 161)
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Published / Filed: **2000-05-16 / 1998-04-14**

Application Number: **US1998000060011**

IPC Code: **A01N 37/18; A61K 9/127; A61K 47/00; C12N 5/08; C07K 17/00;**

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U.S. Class: **514/002; 424/450; 435/176; 435/178; 435/179; 435/180; 435/325; 435/366; 530/300; 530/329; 530/331; 530/811; 530/813; 530/814; 530/815;**

Field of Search: **514/002 424/450 536/051,78,28.2 436/518,528
 530/300,331,329,810,815,811,813,814
 435/174,180,325,366,176,178,179**

Government Interest: This invention was made with government support under grant 1-R01-CA49416 by the National Institutes of Health. The government has certain rights in the invention.

Priority Number:

- 1998-04-14 [US1998000060011](#)
- 1996-08-01 [US1996000691891](#)
- 1995-05-16 [US1995000441770](#)
- 1994-05-19 [US1994000246941](#)
- 1993-10-26 [US1993000142771](#)
- 1992-07-09 [US1992000911209](#)
- 1990-11-01 [US1990000607982](#)

Abstract: Methods and reagents are provided for specifically targeting biologically active compounds such as antiviral and antimicrobial drugs, or prodrugs containing the biologically active compound to specific sites such as specific organelles in phagocytic mammalian cells. The biologically active compound or prodrug is linked to a

microparticle with a linker that is non-specifically or specifically cleaved inside a phagocytic mammalian cell. Alternatively, the biologically active compound or prodrug is impregnated into a porous microparticle or coated on a nonporous microparticle, and then coated with a coating material that is non-specifically or specifically degraded inside a phagocytic mammalian cell. The prodrug contains the biologically active compound linked to a polar lipid such as ceramide with a specific linker such as a peptide that is specifically cleaved to activate the prodrug in a phagocytic mammalian cell infected with a microorganism. A microparticle linked antimicrobial drug or prodrug may be used for killing a microorganism infecting a phagocytic mammalian cell in vivo or in vitro.

❑ Attorney, Agent or Firm:

McDonnell Boehnen Hulbert & Berghoff

❑ Primary / Assistant

Examiners:

❑ INPADOC

Legal Status:

None [Buy Now: Family Legal Status Report](#)

❑ Related Applications:

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Application Number	Filed	Patent	Pub. Date	Title
US1996000691891	1996-08-01	US5840674	1998-11-24	Covalent microparticle-drug conjugates for biological ta
US1995000441770	1995-05-16	US5543391	1996-08-06	Covalent microparticle-drug conjugates for biological ta
US1994000246941	1994-05-19	US5543390	1996-08-06	Covalent microparticle-drug conjugates for biological ta
US1993000142771	1993-10-26	US5543389	1996-08-06	Covalent polar lipid-peptide conjugates for use in salve
US1992000911209	1992-07-09	US5256641	1993-10-26	Covalent polar lipid-peptide conjugates for immunologic targeting
US1990000607982	1990-11-01	US5149794	1992-09-22	Covalent lipid-drug conjugates for drug targeting

❑ Parent Case:

This application is a continuation of application Ser. No. 08/691,891, filed Aug. 1, 1996, now U.S. Pat. No. [5,840,674](#), which is a continuation of application Ser. No. 08/441,770, filed May 16, 1995, now U.S. Pat. No. [5,543,391](#), which is a continuation of application Ser. No. 08/246,941, filed May 19, 1994, now U.S. Pat. No. [5,543,390](#), which is a continuation-in-part of application Ser. No. 08/142,771, filed Oct. 26, 1993, now U.S. Pat. No. [5,543,389](#), which is a continuation-in-part of application Ser. No. 07/911,209, filed Jul. 9, 1992, now U.S. Pat. No. [5,256,641](#), which is a continuation-in-part of application Ser. No. 07/607,982, filed Nov. 1, 1990, now U.S. Pat. No. [5,149,794](#), the disclosures of each of which are herein incorporated by reference in its entirety.

❑ Designated Country:

AM AP BB BG BR BY CA CN CZ EE FI GE HU IS KE KG KP KR KZ LK LR LT LV BE FR GB GR IE IT LI LU MC

Family: [Show 24 known family members](#)

First Claim: [Show all 69 claims](#)

What is claimed is:

1. A composition of matter comprising a prodrug of a biologically-active compound, a microparticle and a cleavable linker moiety comprising two linker functional groups, wherein the cleavable linker moiety has a first end and a second end and wherein the microparticle is attached to the first end of the linker moiety through a first linker functional group and the prodrug attached to the second end of the linker moiety through a second linker functional group, and wherein the cleavable linker moiety is non-specifically cleaved inside a phagocytic mammalian cell, and wherein the prodrug comprises a biologically active compound, a polar lipid moiety comprised of one or a plurality of polar lipid molecules and a specific linker moiety, wherein the specific linker moiety is covalently linked to both the biologically active compound and the polar lipid moiety, wherein the specific linker moiety is specifically cleaved in a phagocytic mammalian cell infected with a microorganism and is specifically activated thereby.

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Buy PDF	Patent	Pub.Date	Inventor	Assignee	Title
	US4780455	1988-10	Liberman et al.	The Trustees of Columbia University in the City of New York	Lipophilic comp pharmacologica organic compou
	US4793986	1988-12	Serino et al.	Johnson Matthey, Inc.	Macromolecula antitumor comp
	US4847240	1989-07	Ryser et al.	The Trustees of Boston University	Method of effec uptake of molec
	US5053394	1991-10	Ellestad et al.	American Cyanamid Company	Targeted forms methyltrithio an agents
	US5149794	1992-09	Yatvin et al.	State of Oregon	Covalent lipid-d conjugates for d targeting
	US5256641	1993-10	Yatvin et al.	State of Oregon	Covalent polar peptide conjugat immunological t
	US5258453	1993-11	Kopecek et al.	University of Utah	Drug delivery sy the simultaneou of drugs activat enzymes and lig
				State of Oregon, Acting by and Through the Oregon State	Covalent polar

 US5543389	1996-08	Yatvin et al.	Board of Higher Education on Behalf of the Oregon Health Sciences University, a non profit organization	<u>peptide conjugates in salves</u>
 US5543390	1996-08	Yatvin et al.	State of Oregon, Acting by and Through the Oregon State Board of Higher Education, Acting for and on Behalf of the Oregon Health Sciences University	<u>Covalent microp drug conjugates biological target</u>
 US5543391	1996-08	Yatvin et al.	State of Oregon, Acting by and Through the Oregon State Board of Higher Education, Acting for and on Behalf of the Oregon Health Sciences University	<u>Covalent microp drug conjugates biological target</u>
 US5840674	1998-11	Yatvin et al.	Oregon Health Sciences University	<u>Covalent microp drug conjugates biological target</u>

Foreign References:

Buy PDF	Publication	Date	IPC Code	Assignee	Title
 EP0077529	1983-04	C07C 93/187	Sanol Schwarz GmbH	<u>Medicinal form</u>	
 EP0109484	1983-04	G08B 21/00	Trampnau, Ulrich	<u>Warning device for helicopters</u>	
 EP0203676	1986-12	A61K 39/12	THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY	<u>Vaccine for generating immunogenic response protecting against a virus</u>	
 EP0279887	1988-08	C07C 101/30	Kesner, Leo	<u>Carnitine direct pharmaceuticals and their use for manufacture of medicament for treatment of metabolic disorder</u>	
 WO8911299	1989-11	A61K 49/00	STATE OF OREGON acting by and through THE STATE ...	<u>METHOD FOR DELIVERY OF THERAPEUTIC AGENTS TO TARGET B TISSUE USING MONOCLONAL ANTIBODY CONJUGATES</u>	
 WO8910348	1989-11	C07C 99/10	GIBBONS, William, Anthony	<u>FATTY AMINO ACID HOMO-ANALOGUE HETERO-OLIGOMERIC CONJUGATES THEREOF</u>	
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 WO9401138	1994-01	A61K 47/48	STATE OF OREGON, acting by and through the OREGON STATE BOARD OF HIGHER EDUCATION on behalf of the OREGON HEALTH SCIENCES UNIVERSITY	COVALENT P LIPID-PEPTID CONJUGATES BIOLOGICAL TARGETING
 WO9402178	1994-02	A61K 47/48	THE GOVERNMENT OF THE UNITED STATES OF AMERICA as	TARGETING O LIPOSOMES T BLOOD-BRAIN BARRIER
 WO9403424	1994-02	C07C 323/41	DRUG DELIVERY SYSTEM INSTITUTE, LTD.	COMPOUND OF INTRACER RESIDENCE A THEREOF
 WO9406450	1994-03	A61K 37/00	UNIVERSTIY OF FLORIDA	BRAIN-ENHAN DELIVERY OF NEUROACTIV PEPTIDES BY SEQUENTIAL METABOLISM
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 WO9522963	1995-08	A61K 9/51	MEDINOVA MEDICAL CONSULTING GMBH	DRUG TARGE SYSTEM, MET PREPARINGS ITS USE
 WO9532002	1995-11	A61K 47/48	STATE OF OREGON, acting by and through THE OREGON STATE BOARD OF HIGHER EDUCATION ON BEHALF OF THE OREGON HEALTH	COVALENT MICROPARTI CONJUGATES BIOLOGICAL TARGETING

				SCIENCES UNIVERSITY	
	WO9604001	1996-02	A61K 38/00	MOLECULAR/STRUCTURAL BIOTECHNOLOGIES, INC.	SITE-SPECIFI BIOMOLECUL COMPLEXES
	WO9622303	1996-07	C07J 5/00	BENDER, Veronika, Judith	THERAPEUTI COMPOUND ACID CONJUG

Other Abstract Info: CHEMABS 118(04)027456V CHEMABS 120(24)307470P CHEMABS 124(14)185548E 125(16)204546S CHEMABS 125(18)230787R CHEMABS 129(25)335730C DERABS C 340298 DERABS C1993-350862 DERABS C1996-020359

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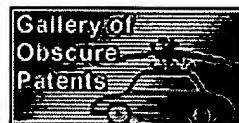
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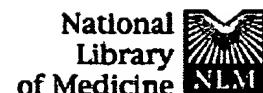
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A lipidated anti-Tat antibody enters living cells and blocks HIV-viral replication.

Cruikshank WW, Doctrow SR, Falvo MS, Huffman K, Maciaszek J, Viglianti G, Raina J, Kornfeld H, Malfroy B.

Pulmonary Center, Boston University School of Medicine, Massachusetts, U.S.A.

We have developed a chemical modification of antibodies, lipidation, which enables their intracellular delivery into living cells. Intracellular localization of lipidated antibodies was demonstrated by confocal microscopy and by measuring cellular uptake of ¹²⁵I-labeled lipidated antibodies. Functionally, lipidated monoclonal antibody directed against the Tat protein from human immunodeficiency virus type 1 (HIV-1) inhibited viral replication of several HIV-1 isolates by approximately 85% as shown by increased viability of infected cells and decreased reverse transcriptase activity. The antibody in its native form had no such effect. These data show that lipidated antibodies can reach and functionally inhibit intracellular targets. Lipidation may help to facilitate the development of intracellular immunotherapy for AIDS.

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NEWS RELEASE

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HIV VIRAL REPLICATION IN LIVING CELLS BLOCKED USING EUKARION ANTIBODY LIPIDATION TECHNOLOGY

(Bedford, MA, April 14, 1997) -- Eukarion, Inc. today announced that it has successfully blocked HIV-1 viral replication in living cells using a monoclonal antibody chemically modified to permit passage across cell membranes. A paper describing these results was published in the March issue of the *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*.

"These findings are important for two reasons," said Bernard Malfroy, Ph.D., Eukarion's chief executive officer. "First, since HIV multiplies rapidly within cells, an approach to halting viral replication could contribute to the development of cell-specific AIDS immunotherapies." The Eukarion antibody targets the HIV-1 "Tat" protein that is required for HIV viral replication. In laboratory experiments using a human lymphocytic cell line, the modified (lipidated) anti-Tat antibody accumulated in HIV-1 infected cells. Once entering the infected cells, the lipidated anti-Tat antibody bound to the Tat protein and blocked its function, leading to suppressed viral replication and, concomitantly, to greatly improved cell survival. The lipidated anti-Tat antibody was found to be effective not only against a laboratory strain of HIV-1, but also against three strains of virus isolated from patients.

"Second and more broadly, we have demonstrated that Eukarion's lipidation technology can facilitate the delivery of antibodies to intracellular targets and that the antibodies retain their binding

specificity and activity," Dr. Malfroy said. "Most monoclonal antibody-based products in development today bind to sites on cell surfaces. With lipidation, we can now use antibodies to target disease-causing substances inside cells and significantly expand the use of monoclonal antibodies for the treatment of human diseases." Eukarion is also evaluating the use of its lipidation technology for other therapeutic applications, and for use with proteins other than antibodies.

The journal article was authored by William W. Cruikshank, Susan R. Doctrow, Melissa S. Falvo, Hardy Kornfeld, Karl Huffmann, Jay Raina and Dr. Malfroy. It represents a collaborative effort between researchers at Eukarion and the Boston University School of Medicine. Dr. Cruikshank, who is Associate Professor of Medicine, directed the principal studies in his laboratory at the B.U. Pulmonary Center.

In addition to its lipidation program, Eukarion has a separate effort underway to develop synthetic catalytic scavenger (SCS) compounds to target reactive oxygen intermediates (ROIs), toxic by-products of tissue stress. ROIs have been implicated in the irreversible damage that occurs in patients suffering from many chronic disorders including asthma, atherosclerosis, lupus, multiple sclerosis, neurodegenerative diseases of the central nervous system, ischemia-induced organ damage, allergy and adult respiratory distress syndrome. These seemingly diverse conditions appear to have ROI involvement as a common link, creating the potential for a small number of SCS compounds to address huge unmet medical needs.

In February 1997, Eukarion signed an agreement with Glaxo Wellcome plc, the world's largest research based pharmaceutical company, for a three year collaborative research and development program for the Eukarion SCS program. The agreement will provide Eukarion scientists with access to Glaxo Wellcome's substantial R&D and screening capabilities and will allow Eukarion to operate at break-even financial levels for the foreseeable future.

Eukarion, Inc., located in Bedford, MA, is a privately held company formed in 1991 to develop proprietary compounds directed against intracellular targets for the treatment of human disease. Eukarion's technologies are protected by issued and pending patent applications owned by the company.



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